REMARKS

Prior to the present submission, claims 22, 38-41, 62, 70, and 76-110 were pending in the application.

In the present submission, claims 31, 62, 70, 78, 89, and 91-110 have been cancelled, and claims 22, 38-41, 76, 77, 83, and 90 have been amended. The amendments to independent claim 22 incorporate the subject matter of claims 39, 89, and 106 into claim 22. The remaining claim amendments are intended to clarify the claimed subject matter for the benefit of the Examiner. Further support for these amendments may be found throughout the specification, for example in paragraphs [0009], [0042], [0104], [0112], [0113], [0135], [0157], [0159], [0184], *etc.* No new matter is introduced by these amendments

Notwithstanding the foregoing, Applicants expressly reserve the right to prosecute subject matter no longer or not yet claimed in one or more applications that may claim priority to the present application.

Reconsideration of the claims is requested in view of the foregoing amendments and the following remarks.

1. 35 U.S.C. § 112, second paragraph

The rejection of claims 22, 38-41, 62, 70, and 76-110 under 35 U.S.C. § 112, second paragraph as allegedly failing to satisfy the definiteness requirement is respectfully traversed.

A first rejection is premised on an assertion that the phrase "defective with respect to" a particular gene is functional language which must be replaced by structural properties defining the claimed bacterium. Applicants strongly disagree that the claims as previously drawn are "insolubly ambiguous" (Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1338–39 (Fed. Cir. 2003) (quoting Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001)), and submit that the claims as previously drawn reasonably apprise those skilled in the art of the scope of the claims.

Notwithstanding the foregoing, Applicants have amended claim 20 to refer to a bacterium which comprises a deletion in the genomic *actA* and *inlB* genes of the bacterium whereby the bacterium does not express ActA or InlB proteins, and a functional genomic *inlA* gene whereby the

bacterium expresses InlA protein. Applicants believe that this language is sufficiently definite as to satisfy the requirements of 35 U.S.C. § 112, second paragraph.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

A further rejection is premised on the assertion that claim 39 "does not make clear whether or not [the antigen] is a heterologous antigen. Office Action, page 3. Applicants submit that the foregoing amendments render this rejection moot.

A further rejection is premised on the assertion that claims 40, 76, 77, 81, 82, and 108 refer to "treating/ protecting against any disease" in a host, but the claims reads solely on the use of an L.monocytogenes bacterium which need not express any heterologous antigen. Bases on this, the Office Action concludes "it appears the bacterium would only be able to treat disease caused by L.monocytogenes." Office Action, page 3. Applicants submit that the rejection is based on an incorrect assertion.

Vaccine compositions may be used to stimulate immunity (mediated by B-cells, T-cells, or both) to an antigen, and/or may be intended to stimulate the innate immune system, which comprises cells and mechanisms that defend the host in a non-specific manner. The innate system recognizes, and responds to, diseases in a generic way and does not confer long-lasting or protective immunity to the host, but does provide immediate short-term defense. It is well established that bacteria, including *Listeria*, stimulate the innate immune system, and can also be used to deliver foreign antigens to stimulate an immune response. Thus, a *Listeria*-based therapeutic may indeed be used in an effort to treat diseases not directly caused by *Listeria.*

Nevertheless, in an effort to advance prosecution, Applicants have amended the claims to refer to *Listeria* bacteria comprising a nucleic acid sequence encoding a polypeptide heterologous to the bacterium operably linked to a promoter sequence directing expression of the heterologous polypeptide by the bacterium.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

2. Obviousness-type double patenting

With regard to the Examiner's provisional rejections for obviousness-type double patenting, Applicants note that no terminal disclaimer is procedurally required in a case where the provisional rejection involves two pending applications and where the rejection is the sole remaining issue in the case. *See*, MPEP 804 (I)(B) (The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in at least one of the applications.") In the event that other rejections of the present claims are successfully overcome by the current communication, withdrawal of the instant provisional rejection would be appropriate. Applicants authorize the examiner to follow MPEP 804 (I)(B) and allow the case without issuing a further Office Action should the provisional obviousness type-double patenting rejection be the sole remaining issue in the case.

3. 35 U.S.C. § 112, first paragraph

The rejection of claims 22, 38-41, 62, 70, and 76-110 under 35 U.S.C. 35 U.S.C. § 112, first paragraph as allegedly failing to satisfy the enablement requirement is respectfully traversed.

The rejection is premised in part on an assertion that the claims encompass various unspecified mutations in the *inlB* or *actA* genes, and that the function of the mutated genes may be reduced by between 25 and 100% relative to the non-mutated gene. Applicants believe that the foregoing amendments render this portion of the rejection moot.

The rejection also asserts that the specification fails to teach which portions of the *inlB* or *actA* genes are critical to their function. While Applicants also believe that the foregoing amendments render this portion of the rejection moot, it is noted that each of these are well known proteins with well established functional domains. *See, e.g.*, Pistor *et al., EMBO J.* 13: 758-63, 1994; Braun *et al., Mol. Microbiol.* 34: 10-23, 1999. One of skill in the art would readily understand those portions of the ActA or InlB molecule relevant to its function.

The rejection further asserts that the specification "has not taught (through challenge experiments) that this bacterium may provide protection (vaccine) or prevent infections caused by

listeria... [and] has not shown that... any bacterium can treat or prevent cancer or any infectious disease." Office Action, page 9.

Respectfully, such assertions represent nothing more than broad allegations that the disclosure is speculative coupled with various difficulties that might be encountered in practice. It is well established in the patent law that a specification is presumed to be enabling. Also, as stated in MPEP § 2164.04, "it is incumbent on the Patent Office... to explain why it doubts any statement in a disclosure, and to back up its assertions of its own with acceptable evidence or reasoning.... Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." Allegations that the specification does or does not "teach through challenge experiments" or "show" certain characteristics do not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g.*, In re Chilowsky, 229 F.2d 457, 463 (CCPA 1956), Ex Parte Hicks, 2000 WL 33673734 at *3.

The present invention does not lie in the use of *Listeria* as a vaccine platform *per se*. Rather, the invention lies in the use of Listeria harboring certain specified mutations as a vaccine platform. *Listeria* has a long history of use as a vaccine platform for both infectious and neoplastic diseases. *See, e.g.,* Ikonomidis *et al.*, Delivery of a Viral Antigen to the Class I Processing and Presentation Pathway by *Listeria monocytogenes*, *J. Exp. Med.* 180: 2209-18 (1994); Pan *et al.*, Regression of Established Tumors in Mice Mediated by the Oral Administration of a Recombinant *Listeria monocytogenes* Vaccine, *Cancer Res.* 55: 4776-79 (1995); Friedman *et al.*, Induction of Human Immunodeficiency Virus (HIV)-Specific CD8 T-Cell Responses by *Listeria monocytogenes* and a Hyperattenuated *Listeria* Strain Engineered To Express HIV Antigens, *J. Virol.* 74: 9987-93 (2000); Angelakopoulos *et al.*, Safety and Shedding of an Attenuated Strain of *Listeria monocytogenes* with a Deletion of actA/plcB in Adult Volunteers: a Dose Escalation Study of Oral Inoculation, *Infect. Immun.* 70: 3592-3601 (2002); Pardoll, Spinning Molecular Immunology into Successful Immunotherapy, Nature Rev. 2: 227- 38 (2002); Blattman *et al.*, Cancer Immunotherapy: A Treatment for the Masses, *Science* 305: 200-5 (2004); Lara-Tejero and Pamer, T-cell Responses to *Listeria monocytogenes*, *Curr. Opin. Microbiol.* 7: 45-50 (2004).

The immune response initiated by a vaccine may or may not ultimately be protective to the recipient; indeed, seronegativity following vaccination may be a problem even with common

vaccines for diseases such as measles and varicella. The fact that vaccines may not be protective in any and all cases and for any and all diseases does not mean that the practice of such a method is somehow not enabled. It is likely that most claims will encompass certain inoperable embodiments. For example, vaccines may also be unlikely to work if exposed to high temperatures or extremes of pH, as harsh conditions such as these are not particularly hospitable to biological materials. But, as the Board of Patent Appeals and Interferences has repeatedly pointed out in the context of enablement rejections, it is not the task of the claims to exclude such potentially inoperable embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984) ("Nor are we concerned that the claims may include inoperable embodiments, as is it not a function of the claims to specifically exclude possible inoperative embodiments").

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

4. 35 U.S.C. § 103

The rejection of claims 22, 31, 38-40, 62, 70, 77, 81, 83, and 89 under 35 U.S.C. 103(a) as allegedly being unpatentable over Appelberg *et al., Infect. Immun.* 68: 912-14 (2000) is respectfully traversed.

The claims as presently amended refer to a bacterium which comprises (a) a deletion in the genomic *actA* and *inlB* genes of the bacterium whereby the bacterium does not express ActA or InlB proteins, (b) a functional genomic *inlA* gene whereby the bacterium expresses InlA protein, and (c) a nucleic acid sequence encoding a heterologous polypeptide which the bacterium also expresses. As discussed below, Appelberg *et al.* does not suggest deleting both *actA* and *inlB* in the context of retaining *inlA*. Nor does Appelberg *et al.* suggest that such a strain would have any value in delivery of a heterologous polypeptide to a host.

The Appelberg *et al.* publication discloses *Listeria* strains attenuated by deleting the entire *inlA/B* operon, and separate strains attenuated by deleting the *actA* gene. The rejection notes that Appelberg *et al.* states that "it will be interesting to analyze the characteristics of double mutants defective in both the ActA and the internalin pathways." Office Action, page 13.

But the conclusion drawn in the Office Action, that one of ordinary skill in the art would have been motivated from Appelberg *et al.* to produce a mutant deficient in both *actA* and *inlB*, is not completely accurate, and is based on a false assumption.

Appelberg *et al.* does not delete *inlB* in isolation; Appelberg *et al.* deletes the entire *inlA/B* operon. Thus, while one of skill in the art might arguably have been motivated from the Appelberg *et al.* to produce a mutant deficient in both *actA* and *inlA/B* (a point Applicants do not concede), one would not have been motivated to produce a mutant deficient in *actA* and *inlB* while leaving *inlA* intact.

Appelberg *et al.* is interested in understanding the role of *actA* and the internalin operon in hepatocyte invasion by *Listeria* purely as an "interesting" scientific matter. While Appelberg *et al.* understands that that *actA* and *inlA/B* are each involved in hepatocyte invasion, Appelberg *et al.* is not interested in the use of *Listeria* mutants for treatment of "virulent infection" by *Listeria*. Indeed, nothing of record in the rejection indicates that a mutated *Listeria* strain deficient in hepatocyte invasion could or should be used to treat an ongoing *Listerial* infection. Nor does the Office Action explain why one skilled in the art would have believed that a mutant deficient in both *actA* and *inlA/B* could have been used therapeutically or to "find a way of treating" a *Listeria* infection, or even how this might have been done. Instead, the conclusion in the Office Action that one would have been motivated to produce a mutant deficient in both *actA* and *inlA/B* "in order to find a way of treating such a virulent infection" (Office Action, page 14) is completely without support from the record. Moreover, if one had as a goal "creat[ing] a less infective/pathogenic microorganism" (*id.*), one would not be led to delete both *actA* and *inlB*, but retain *inlA*, as in the present claims.

As demonstrated by Applicants, the claimed *Listeria* strains actually present a number of practical advantages as a vaccine platform that are not readily apparent from the cited art. The claimed *Listeria* strains retain the immune response-inducing capacity of *Listeria*, and thus the ability of the vaccine platform to access phagocytic cells (*e.g.*, antigen presenting cells such as

dendritic cells and macrophages), requisite steps in eliciting a robust adaptive immune response. The claimed strains also delete/diminish toxicity-inducing capacity, by preventing InlB/HGFR-mediated uptake in hepatocytes and InlB/heparin sulfate mediated uptake, a glycosaminoglycan that is ubiquitously expressed on somatic cells that are not necessarily immune cells required to elicit an adaptive immune response. The claimed strains also prevent the infection of hepatocytes indirectly via ActA-mediated cell to cell spread. Thus, the claimed *Listeria* strains offer dramatic improvement in hepatic clearance relative to deletion of *actA* or *inlB*, while retaining the ability to generate a productive immune response.

It is also worth noting that the Listeria strain which deletes *actA* and *inlB* but retains *inlA* provides dramatically improved antigen-specific cytotoxicity when administered intravenously (Specification, table 2). In addition, retention of *inlA* permits the claimed vaccine strain to retain mucosal uptake, thus providing an attenuated strain that can be used as both an oral and intravenous vaccine vector.

Applicants respectfully submit that, in view of the foregoing, no *prima facie* case of obviousness has been established. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103 be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that all rejections and objections have been obviated and that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 203-3186.

Respectfully submitted,

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